AAC Journals.ASM.org

Switching from Posaconazole Suspension to Tablets Increases Serum Drug Levels in Leukemia Patients without Clinically Relevant Hepatotoxicity

Dong Sik Jung,[a,c] Frank P. Tverdek,[b] Dimitrios P. Kontoyiannis[a]

Departments of Infectious Diseases, Infection Control, and Employee Health[a] and Pharmacy Clinical Programs,[b] The University of Texas MD Anderson Cancer Center, Houston, Texas, USA; Division of Infectious Diseases, Department of Internal Medicine, Dong-A University College of Medicine, Busan, South Korea[c]

We evaluated posaconazole serum concentrations and hepatotoxicity in 12 leukemia patients who transitioned from posaconazole suspension to tablets. Patients who switched to tablets had significantly increased posaconazole concentrations (median: suspension, 748 ng/ml; tablet, 1,910 ng/ml; $P < 0.01$) without clinically relevant hepatotoxicity.

Despite concerns of poor bioavailability, posaconazole (POSA) suspension has been used effectively as prophylaxis and as a salvage treatment of invasive fungal infections with rare clinical hepatotoxicity (1). Higher serum concentrations of POSA suspension were associated with higher response rates in treatment of invasive aspergillosis (2). Recent studies (3–6) have suggested that the absorption of the new formulation of POSA delayed-release tablets is minimally affected by food, mucositis, or increased gastric pH and impaired motility and that the new tablet formula also attains higher average concentrations than the suspension does and is well tolerated in healthy subjects. However, no studies about patients who were "bridged" from POSA suspension to tablets have been published to date. We report our early experience in leukemia patients who switched from POSA suspension to delayed-release tablets.

Pharmacy databases were queried for adult cancer (>18 years of age) patients who were switched from POSA suspension (400 mg twice daily or 200 mg 4 times daily) to tablets (300 mg once daily) at The University of Texas MD Anderson Cancer Center from December 2013 to January 2014. Once POSA tablets were added to the formulary, a general trend seen in our hematologic malignancy patient population was that physicians would independently transition almost all current and future patients to tablets despite suspension remaining on the formulary. We identified 12 patients with leukemia who were treated as such. Validated high-performance liquid chromatography (HPLC) assay-tandem mass spectrometry (performed at Mayo Clinic Department of Laboratory Medicine and Pathology, Rochester, MN) was used to measure posaconazole concentrations in blood (7). All patients who had serum POSA levels recorded during both the POSA suspension and tablet periods were identified. POSA concentrations were included in the analysis only if the data were obtained 7 days after POSA administration, as steady state of the drug should be reached at this time for both suspension and tablet (4, 8). The patients' medical records were reviewed for demographic, clinical, and laboratory characteristics (Table 1). Target serum POSA levels were defined as greater than 700 ng/ml for prophylaxis and greater than 1,000 ng/ml for treatment (9). Clinically relevant

TABLE 1 Baseline demographic and clinical characteristics of the 12 leukemia patients switched from posaconazole suspension to delayed-release tablets

Variable[d]	Value
Median age, yr (range)	58 (25–73)
Male sex, *n* (%)	8 (67)
Body wt, kg	
Mean (SD)	74.2 (21.7)
Median (range)	72.4 (51–128)
Median ht, cm (range)	174.5 (159–193)
Underlying hematologic malignancy, *n* (%)	
Acute myeloid leukemia	8 (67)
Acute lymphoblastic leukemia	2 (17)
Chronic myeloid leukemia	1 (8)
Chronic lymphocytic leukemia	1 (8)
HSCT, *n* (%)	5 (42)
Underlying condition at the time of sampling,[a] *n* (%)	
ANC of <500/μl	6 (50)
Graft-versus-host disease	3 (25)
Mucositis, ≥grade 2[b]	1 (8)
Diarrhea, ≥grade 2[b]	4 (33)
Concomitant PPI or H2 antagonist	6 (50)
Concomitant tacrolimus	5 (42)
GFR of <50 ml/min/1.73 m^2	3 (25)
Indication for posaconazole, *n* (%)	
Prophylaxis	3 (25)
Presumed or documented fungal infection (species identified)[c]	9 (75)

[a] For measurement of serum POSA levels.
[b] National Cancer Institute, Common Terminology Criteria for Adverse Events, version 4.0, 2010, accessed at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (10).
[c] Identified fungal organisms: *Aspergillus*, 1; *Zygomycetes*, 3; *Fusarium*, 2.
[d] Abbreviations: SD, standard deviation; ANC, absolute neutrophil count; HSCT, hematopoietic stem cell transplantation; PPI, proton pump inhibitor; GFR, glomerular filtration rate.

Received 5 August 2014 **Returned for modification** 25 August 2014
Accepted 31 August 2014
Published ahead of print 8 September 2014
Address correspondence to Dimitrios P. Kontoyiannis, dkontoyi@mdanderson.org.

doi:10.1128/AAC.04035-14

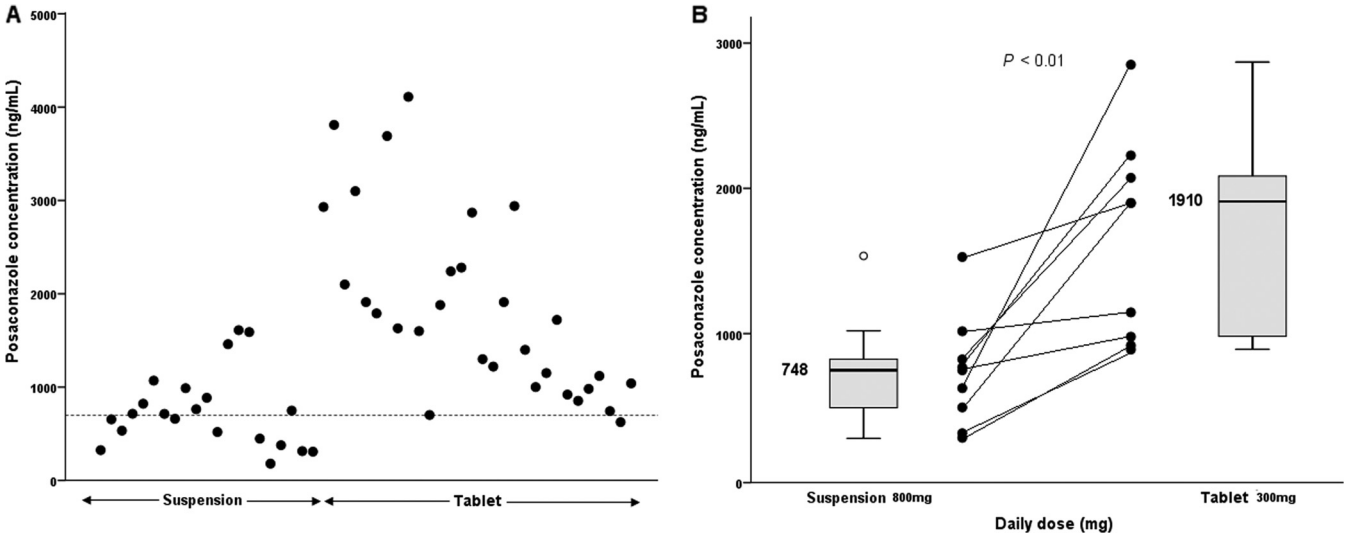

FIG 1 (A) Distribution of serum POSA levels in 12 leukemia patients showing higher levels when these patients received POSA tablets (right) than when the patients received suspension (left). The dotted line depicts the target level for prophylaxis (>700 ng/ml). (B) Comparative measurements in 9 leukemia patients. Three patients were excluded either because the serum levels were measured too early or because of missing data. The black line in the box and corresponding concentrations represent the median serum POSA levels. The black line between dots depicts an increased change of median concentration for each patient who switched from suspension to tablets.

hepatotoxicity, mucositis, and diarrhea were defined according to the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0) (10). The study was approved by the Institutional Review Board of the MD Anderson Cancer Center.

Six of the 12 patients had neutropenia (absolute neutrophil count, <500/μl). Five had undergone hematopoietic stem cell transplantation, and 3 had graft-versus-host disease (GvHD). Nine (75%) patients received POSA tablets for treatment of a documented fungal infection, and 3 (25%) patients received POSA tablets for prophylaxis (Table 1).

We included 21 suspension and 30 tablet levels in the analysis. When the patients received POSA tablets, target POSA levels for prophylaxis (>700 ng/ml) and for treatment (>1,000 ng/ml) were reached in 29 of 30 (97%) serum levels and in 25 of 30 (83%), respectively. When patients received POSA suspension, only 12 of 21 (57%) serum levels reached target levels for prophylaxis, and only 5 of 21 (24%) reached target levels for treatment (Fig. 1A).

Comparative measurements were available for 9 patients, as 3 were excluded either because the serum levels were measured too early or because of missing data. Patients had higher median POSA serum concentrations (1,910 ng/ml) during the POSA tablet period than during the POSA suspension period (748 ng/ml) ($P < 0.01$). The POSA serum concentration significantly increased in 9 patients after they switched from the suspension to tablets ($P < 0.01$, Wilcoxon signed-rank test) (Fig. 1B). GvHD, diarrhea, and acid-suppressing agents, all of which are known to decrease serum POSA suspension (9, 11, 12), were not associated with reduction of the median serum POSA concentration below 1,000 ng/dl in the patients when they received the POSA tablets ($P > 0.05$, Fisher exact test).

Five of the 9 patients who had normal baseline liver function tests (LFTs) when starting POSA tablets had mild, asymptomatic increases in LFTs (CTCAE grade 2 or less) 7 days after POSA tablet treatment. Total bilirubin elevation constituted the majority of these abnormalities (80%). The liver enzymes returned to the normal range within 3 weeks, even though patients continued to receive POSA tablets. Of the 3 patients who had abnormal LFTs, 2 patients had decreased liver enzyme levels after taking POSA tablets; only one patient, who had severe GvHD (skin, liver, grade 3), experienced sustained and increased LFTs in spite of discontinuation of POSA tablets. It is unclear what the POSA contributed to increased LFTs in the setting of existing liver GvHD. As such, POSA tablets were well tolerated in our patients.

Our study is the first to evaluate serum POSA concentration differences and hepatotoxicity associated with transitioning from POSA suspension to tablets in high-risk patients with leukemia. We found that switching from POSA suspension to tablets reliably resulted in increased serum POSA levels, which supports the findings of a similar study in healthy subjects (4) and a phase 1B/3 study in leukemic patients (6). Our patients did not experience treatment-limiting hepatotoxicity as a result of the increased serum POSA levels.

Our findings suggest that for prophylaxis or treatment of invasive fungal infections in this severely ill population, POSA tablets are better absorbed than is POSA suspension in accordance with previous studies (3–6). When patients received POSA suspension, their serum POSA levels poorly reached prophylactic and treatment target levels. However, when patients were switched to POSA tablets, serum POSA levels significantly increased, reaching both prophylactic and treatment target levels (Fig. 1). Moreover, regardless of potential variables affecting absorption (11, 12), most of the serum POSA levels measured when the patients received the tablets reached target levels similar to results of recent studies in both healthy subjects (3–5) and a patient with leukemia (6) and were higher than the serum levels measured when the patients received POSA suspension and did not cause clinically relevant hepatotoxicity.

In conclusion, our preliminary experience suggests that POSA tablets switched from suspension were well absorbed, tolerated, and safe in patients with hematologic cancer. Future studies with

larger numbers of patients may be needed to clarify a relationship between POSA serum level and hepatotoxicity.

ACKNOWLEDGMENTS

We thank Francisco Ponce (University of Houston College of Pharmacy) and Yunlu Zhu (University of Texas College of Pharmacy) for useful information.

D.P.K. is a recipient of the Frances King Black Endowment.

No financial support was received.

D.P.K. has received research support and honoraria from Pfizer; Astellas Pharma US; Gilead Sciences, Inc.; and Merck & Co., Inc. All other authors report no potential conflicts.

REFERENCES

1. **Leventakos K, Lewis RE, Kontoyiannis DP.** 2010. Fungal infections in leukemia patients: how do we prevent and treat them? Clin. Infect. Dis. **50:**405–415. http://dx.doi.org/10.1086/649879.
2. **Walsh TJ, Raad I, Patterson TF, Chandrasekar P, Donowitz GR, Graybill R, Greene RE, Hachem R, Hadley S, Herbrecht R, Langston A, Louie A, Ribaud P, Segal BH, Stevens DA, van Burik J-AH, White CS, Corcoran G, Gogate J, Krishna G, Pedicone L, Hardalo C, Perfect JR.** 2007. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin. Infect. Dis. **44:**2–12. http://dx.doi.org/10.1086/508774.
3. **Krishna G, Ma L, Martinho M, O'Mara E.** 2012. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrob. Agents Chemother. **56:**4196–4201. http://dx.doi.org/10.1128/AAC.00222-12.
4. **Krishna G, Ma L, Martinho M, Preston RA, O'Mara E.** 2012. A new solid oral tablet formulation of posaconazole: a randomized clinical trial to investigate rising single- and multiple-dose pharmacokinetics and safety in healthy volunteers. J. Antimicrob. Chemother. **67:**2725–2730. http://dx.doi.org/10.1093/jac/dks268.
5. **Kraft WK, Chang P, van Iersel ML, Waskin H, Krishna G, Kersemaekers W.** 2014. Posaconazole tablet pharmacokinetics: lack of effect of concomitant medications altering gastric pH and gastric motility in healthy subjects. Antimicrob. Agents Chemother. **58:**4020–4025. http://dx.doi.org/10.1128/AAC.02448-13.
6. **Duarte RF, López Jiménz J, Cornely OA, Ma L, van Iersel MPS, Waskins H.** 2012. Phase 1B study of the pharmacokinetics and safety of posaconazole (POS) solid oral tablet in patients at risk for invasive fungal infection (IFI), abstr. A-1934. Abstr. 52nd Intersci. Conf. Antimicrob. Agents Chemother.
7. **Shen JX, Krishna G, Hayes RN.** 2007. A sensitive liquid chromatography and mass spectrometry method for the determination of posaconazole in human plasma. J. Pharm. Biomed. Anal. **43:**228–236. http://dx.doi.org/10.1016/j.jpba.2006.06.011.
8. **Heinz WJ, Zirkel J, Kuhn A, Schirmer D, Lenker U, Keller D, Klinker H.** 2011. Relevance of timing for determination of posaconazole plasma concentrations. Antimicrob. Agents Chemother. **55:**3621–3623. http://dx.doi.org/10.1128/AAC.00062-11.
9. **Ashbee HR, Barnes RA, Johnson EM, Richardson MD, Gorton R, Hope WW.** 2014. Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. J. Antimicrob. Chemother. **69:**1162–1176. http://dx.doi.org/10.1093/jac/dkt508.
10. **National Cancer Institute.** 2009. Common terminology criteria for adverse events (CTCAE), v4.0. National Cancer Institute, Bethesda, MD.
11. **Dolton MJ, Ray JE, Chen SC, Ng K, Pont L, McLachlan AJ.** 2012. Multicenter study of posaconazole therapeutic drug monitoring: exposure-response relationship and factors affecting concentration. Antimicrob. Agents Chemother. **56:**5503–5510. http://dx.doi.org/10.1128/AAC.00802-12.
12. **Crombag MR, Huisman C, Kemper EM, Bruggemann R, Bijleveld YA.** 2012. Posaconazole treatment in hematologic patients: a pilot study of therapeutic drug monitoring. Ther. Drug Monit. **34:**320–325. http://dx.doi.org/10.1097/FTD.0b013e31824d135c.